DEPARTMENT OF
HEALTH, EDUCATION, AND W[illegible] AF[illegible]
~~FEDERAL SECURITY AGENCY~~
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37

IN REPLYING, ADDRESS THE
NIMH Addiction Research Center.

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Our experiments on tolerance to LSD-25 have been proceeding well, although I continue to be somewhat surprised by the results, which to me are the most amazing demonstration of drug tolerance I have ever seen. I have had 7 patients who have now been taking the drug for more than 42 days. One of these patients receives 1 mcgm./kg. daily, 4 receive 1.5 mcgm./kg. daily, and 2 receive 2 mcgm./kg. daily. All 7 are quite tolerant to both the physiological and mental effects of the drug.

We have attempted to break through this tolerance by administering double, triple and quadruple doses. We have not yet observed full restoration of the LSD-effect with any of these doses, which, in the case of one of the patients receiving 2 mcgm./kg. daily, amounted to 532 mcgm. total dose. Increasing the dose seems to restore the physiological effects to a greater degree than the mental effects, which are present in only mild degree and which do not persist for more than one or two hours. Discontinuation of the drug for two days in one patient was followed by almost complete restoration of the initial effect. Administration of 200 mg. of the metabolic blocker, SKF-525, did not overcome the tolerance.

We have also been attempting to study "antidotes" for LSD-25. We have done quite a number of experiments in which 0.2 Gm. of pentobarbital was given 30 minutes prior to LSD. This drug appears to definitely alter the LSD reaction, in that anxiety, nervousness, and insomnia are markedly reduced. However, the price paid is that of partial drunkeness induced by the barbiturate.

We have completed two experiments with Corynanthine. The patients used were extremely sensitive subjects who gave grade 3 to 4 reactions to a 40-mcgm. dose of LSD-25. They were given

A-13

In a randomized order 15 mg. Corynanthine followed by placebo; placebo followed by 40 mcgm. LSD; Corynanthine, 15 mg., followed by 40 mcgm. LSD. There was no evidence of any diminution in either the mental or physiological effects of the LSD. Other experiments are to be done, using less sensitive subjects.

As yet we have not had an opportunity to try Banthine.

While in Washington recently, I had a very interesting visit with Dr. Edward Evarts who is working with LSD and Bufontenine. As you know, he has been able to demonstrate very definite effects of both drugs in dogs and monkeys. As a result of this, neurophysiological studies have been undertaken. These include the effects of LSD on peripheral nerves. In the frog, LSD apparently raises the threshold but does not change height of the action potential once the threshold is crossed. Other neurophysiological work is concerned with the effects of LSD on the entire optical tract, from the optic nerve all the way back to the optical cortex. Apparently some kind of results are being obtained, but as yet they are not clear-cut. Other statements include one that, in human subjects, LSD caused marked slowing of simple reaction time, but had little effect on flicker fusion frequency.

Dr. Cholden, a member of the NIMH staff and who is using LSD in the treatment of psychotic patients, sought me out while I was in Bethesda. He has apparently observed the development of tolerance to LSD in these psychotic patients. Because of the development of tolerance, he alternates LSD and mescaline. He states there is no cross tolerance to these two drugs.

We recently obtained a small supply of an interesting substance in the cannabinol series which appears to be extremely potent. I have now given 11 subjects doses of 1 to 2.5 mg. of this drug. The first 2 patients promptly identified the effects as being like those of marihuana and, naturally, all patients since the first 2 have expected marihuana-like effects. Patients begin to report the subjective effects within 2 to 4 hours. Effects appear to be most prominent 6 to 8 hours after the drug is administered and are still present 24 to 36 hours later; and in some cases even longer. Description of the subjective effects is very vague, except that the subjects are very positive they resemble those of marihuana. They say the effects of 1 mg. are equal to one or two cigarettes of the best marihuana, except that they appear slowly and persist for a

very long period of time. They are described as consisting of a sensation of mental relaxation accompanied, however, by "physical" tension, increased appreciation of music, jokes, and other things. The characteristic behavior observed in marihuana smokers (giggling, silliness) has not been seen, but the experimental situation has not been conducive to the appearance of such behavior. No hallucinations, perceptual distortion, etc., have been reported.

With larger doses (2 to 2.5 mg.) the symptoms became quite unpleasant in 6 of the 11 subjects 6 to 8 hours after administration. The unpleasant symptoms included dizziness, feeling of great weakness, marked drowsiness, nausea and vomiting. Weakness has persisted for 48 to 72 hours after administration of the drug. One patient fainted on going to the bathroom the morning after having received a 2-mg. dose.

Neurological examination in these patients so far has been negative with the doses used. However, gait could not be tested in some patients who became so weak they refused to get out of bed. There is a very definite tendency for the pulse rate to become rapid and a tendency for the blood pressure to fall. The results suggest that some cardiovascular disturbance, possibly postural hypotension, may occur. I hope to investigate this in the immediate future. Because of the appearance of these toxic reactions, I am not planning to increase the dose beyond 2.5 mg., in the immediate future.

It is noteworthy that the patients show the characteristic marihuana facies, which consist chiefly of marked conjunctival reddening and pseudoptosis.

I hope soon to have some information on Bufotenine, but have not carried out any experiments as yet.

Sincerely yours,

Harris Isbell

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A-132